REMARKS

Claims 1-7, 11, 13-14, and 16-36 were pending in the instant application. Claims 1-6, 11, and 17-28 have been withdrawn without prejudice as being drawn to non-elected subject matter. Claims 7 and 14 have been amended to specifically point out and distinctly claim that which the Applicants regard as the invention. Claim 16 has been amended to provide antecedent basis. Claims 33 and 35 have been amended to correct a typographical error. New claims 37-49 have been added. Support for the amendments can be found in the specification, for example, at paragraphs [0014] page 2, line 60 left column to line 11 right column, [0016] page 2, lines 42-48 right column, [0041], [0115] page 12, lines 2-4 right column, [0116] page 12, lines 38-40 right column, [0117], [0118], [0254] page 28, lines 50-56 left column, and [0508] page 54, line 33 left column to line 4 right column. No new matter has been added.

As such, claims 7, 13-14, 16 and 29-49 are pending. Applicants respectfully request entry of the foregoing amendments and following remarks into the record of the instant application.

1. DISCLAIMING PRIORITY TO RELATED U.S. APPLICATIONS

Applicants hereby disclaim priority of the present application to parent Application Serial No. 09/385,219, filed on August 27, 1999, now U.S. Patent No. 6,720,181 and Provisional Application No. 60/098,355, filed on August 28, 1998; Provisional Application No. 60/118,568, filed February 3, 1999; and Provisional Application no. 60/124,449, filed on March 15, 1999. The specification has been amended to delete Cross-Reference to related U.S. Application.

2. SEQUENCE COMPLIANCE

The Examiner has indicated that in order to perfect sequence compliance, Applicant should submit an amendment to the specification directing entry of the substitute sequence listing paper copy filed on February 8, 2007. The specification has been amended to direct entry of the substitute sequence listing. Accordingly, sequence compliance is hereby perfected.

3. REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH SHOULD BE WITHDRAWN

Claims 7, 13-14, 16, and 29-36 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, the Examiner alleges that claims 7, 13 (and claims 29, 31, 33, and 35 dependent therefrom), claims 14, and 16 (and claims 30, 32, 34, and 36 dependent therefrom) are indefinite in the recitation of "FBP1" and "βTrcp2". According to the Examiner, the scope of "FBP1" and "βTrcp2" proteins have the function of targeting IκBα for degradation and the scope of FBP1 proteins is structurally limited to those encoded by SEQ ID NO:1 and hybridizing variants thereof or βTrcp2 with "minor variations", the claims do not appear to so limit the function and structure of the members of the genus. The Examiner further alleges that the specification discloses functionally altered FBP gene products which may alter one or more of the biological functions of the FBP gene product.

Applicants submit that it is clear from the specification that the FBP1 protein includes those gene products encoded by the FBP1 gene sequences which comprise nucleic acid molecules containing the DNA sequences of SEQ ID NO:1 and nucleic acid molecules that can hybridize to the DNA sequence of FBP1 under moderately stringent conditions (*see, e.g.*, published application at paragraphs [0115], page 12, lines 2-4 right column, [0116] page 12, lines 38-40 right column, and [0118]). Claim 7 has been amended to recite that the FBP1 and ßTrcp2 comprise at least one biological activity of endogenous FBP1 and ßTrcp2, respectively. Claim 14 has been amended to recite, in part, methods for screening compounds using F-box Protein 1 ("FBP1") having an amino acid sequence of SEQ ID NO:2 or wherein said FBP1 is encoded by a nucleic acid molecule that hybridizes under moderately stringent conditions to the complement of a nucleic acid sequence of SEQ ID NO:1. One skilled in the art would understand the bounds of the claim when read in light of the specification. As such, the claims recite FBP1 and ßTrcp2 that have the desired structure and function.

New claim 37 and its dependent claims, claims 38-42; and claim 44 and its dependent claims, claims 44-48 have been added to recite, in part, methods for screening compounds using F-box protein ("FBP1") having an amino acid encoded by the FBP1 gene sequences which comprise nucleic acid molecules containing the DNA sequences of SEQ ID NO:1 and

nucleic acid molecules that can hybridize to the DNA sequence of FBP1 under highly stringent conditions (*see, e.g.*, published application at paragraphs [0117]). Accordingly, Applicants submit that claims 7, 13-14, 16, and 29-36, and new claims 37-48 are definite.

The Examiner alleges on page 5 of the final Office Action that prior art recognizes at least two other proteins as "Fbp1" (*i.e.*, floral binding protein 1, fat body protein) (page 5 of the Office Action dated August 8, 2006). The Examiner alleges that it is unclear as to how a skilled artisan distinguishes an "FBP1" protein from other FBP proteins, *e.g.*, "FBP2", "FBP3", "FBP4", *etc.* Claims 7 and 14 have been amended to recite, in part, a method for screening compounds using a cell or cell extract comprising an F-box protein ("FBP1") having an amino acid sequence of SEQ ID NO:2 or wherein said FBP1 is encoded by a nucleic acid molecule that hybridizes under moderately stringent conditions to the complement of a nucleic acid sequence of SEQ ID NO:1. Applicants submit that FBP1, FBP2, FBP3, and FBP4 are distinguished from each other by their amino acid sequences. Each FBPs amino acid sequence and nucleic acid sequence encoding it is disclosed in the published application (*See, e.g.*, [0046], [0048]-[0073], FIG. 1, FIG.2 and the substitute sequence listing). Applicants further submit that since the specification does not teach floral binding protein 1 or fat body protein and teaches that FBP1 is F-box protein 1, one skilled in the art would understand the bounds of the claim when read in light of the specification.

The Examiner further alleges that claim 14 and its dependent claims 16, 30, 32, and 36 are indefinite because claim 14 recites "the FBP1 or ßTrcp2 activity comprises degradation of IκBα." The Examiner alleges that while the specification acknowledges the activity of FBP1 or ßTrcp2 as interacting with IκBα and that an activity of FBP1 or ßTrcp2 is promoting degradation of IκBα, there is no indication that the activity of FBP1 or ßTrcp2 is degradation of IκBα. As discussed above, claim 14 has been amended to recite that the FBP1 and ßTrcp2 are capable of promoting the degradation of IκBα.

In view of the foregoing remarks and claim amendments, Applicants respectfully request that the rejection of claims 7, 13-14, 16, and 29-36 under 35 U.S.C. § 112, second paragraph, be withdrawn.

4. REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH SHOULD BE WITHDRAWN

A. Rejection for Lack of Written Description Should Be Withdrawn

Claims 7, 13-14, 16, and 29-36 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Examiner alleges that the recitation "the FBP1 or ßTrcp2 activity comprises degradation of IκBα" in claim 14 lacks support in the specification (page 6-7 of the final Office Action). As discussed above, claim 14 have been amended to recite, in part, that the FBP1 and ßTrcp2 are capable of promoting the degradation of IκBα. The Examiner further alleges that the claims are not limited to the members of the genus which have the function of targeting IκBα for degradation and are structurally limited to FBP1 proteins encoded by SEQ ID NO:1 and any amino acid sequence encoding SEQ ID NO:2. The Examiner also alleges that prior art acknowledges the existence of multiple FBP proteins and it is unclear as to how a skilled artisan distinguishes an "FBP1" protein from "FBP2", "FBP3", "FBP4", *etc.* (page 8-9 of the final Office Action).

The factual inquiry of whether there is sufficient written description under 35 U.S.C. § 112 is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, Applicant was in possession of the invention as now claimed. *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, 19 USPQ 2d 1111, 1117 (Fed. Cir. 1991). Disclosure of sufficiently detailed, relevant identifying characteristics, *i.e.*, structure, physical, and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or combination of such characteristics can provide evidence that Applicant was in possession of the claimed invention. *Enzo Biochem, Inc. v. Gen-Probe, Inc.*, 323 F.3d at 964, 63 USPQ2d at 1613 (Fed. Cir. 2002).

Claims 7 and 14 have been amended to recite, in part, methods for screening compounds using F-box Protein 1 ("FBP1") having an amino acid sequence of SEQ ID NO:2 or wherein said FBP1 is encoded by a nucleic acid molecule that hybridizes under moderately stringent conditions to the complement of a nucleic acid sequence of SEQ ID NO:1. Claim 7 has been amended to recite that the FBP1 and ßTrcp2 comprise at least one biological activity of endogenous FBP1 and ßTrcp2, respectively, and claim 14 has also been amended to recite FBP1 and ßTrcp2 which are capable of promoting the degradation of IκBα. Applicants submit that the instant specification provides sufficient written description for the species

encompassed by FBP1. New claim 37 and its dependent claims, claims 38-42; and claim 44 and its dependent claims, claims 44-48 have been added to recite, in part, methods for screening compounds using F-box protein ("FBP1") having an amino acid encoded by the FBP1 gene sequences which comprise nucleic acid molecules containing the DNA sequences of SEQ ID NO:1 and nucleic acid molecules that can hybridize to the DNA sequence of FBP1 under highly stringent conditions. For example, the instant specification teaches that the FBP1 protein includes those gene products that comprise: (a) an amino acid sequence of SEQ ID NO:2 (published application paragraph [0154]; (b) encoded by the FBP1 gene sequences of SEQ ID NO:1 (published application paragraph [0115], page 12, lines 2-4 right column); (c) encoded by a nucleic acid sequence that encodes a polypeptide of SEQ ID NO:2 (published application paragraph [0116], page 12, lines 38-40 right column); (d) encoded by a nucleic acid sequence that hybridize under highly stringent conditions to the complement of the nucleic acid sequence comprising SEQ ID NO:1 (published application paragraph [0117]; and (e) encoded by a nucleic acid sequence that hybridize under moderately stringent conditions to the complement of the nucleic acid sequence comprising SEQ ID NO:1 (published application paragraph [0118]). Such methods of hybridization are well know in the art, published application paragraph [0118], citing to Ausebel *et el.*, eds., 1989, Current Protocols in Molecular Biology, Vo*l.* 1, Green Publishing Associates, Inc., and John Wiley & Son, Inc., New York, at p. 2.10.3). Expression of a gene product from nucleic acid sequence, including using recombinant DNA technology is also well known in the art. Accordingly, the instant specification provides clear written description for the species encompassed by FBP1.

Applicants further submit that the instant specification provides clear written description for the species encompassed by βTrcp2. The instant specification incorporates in its entirety Koike *et al.*, 2000, *Biochem. Biophys. Res. Comm.*, 269:103-109 ("Koike"), which discloses the DNA sequences and amino acid sequences of three isoforms of βTrcp2 (*see, e.g.*, published application at paragraph [0016]). One skilled in the art would know that minor variations in the sequence of βTrcp2 will still yield βTrcp2 species and can test their function using the assay for determining IκBα degradation provided in the specification. As such, the specification provides adequate written description for the presently claimed invention.

Furthermore, the specification also teaches assays for determining FBP1 and ßTrcp2 activities, such as, involving in IκBα degradation (published application at paragraphs [0470] and [0471], Section 13.1 IκBα degradation experiments). One skilled in the art would have

known that not all FBP1 and ßTrcp2 gene products are encompassed by the claims – only those FBP1 and ßTrcp2 gene products that comprise at least one biological activity of endogenous FBP1 and ßTrcp2 (for claim 7); or those FBP1 and ßTrcp2 gene products that are capable of promoting IκBα degradation (for claim 14) are useful for the claimed methods. Since the specification provides a test for the species of FBP1 and ßTrcp2 gene products that are useful for the methods of the invention, one skilled in the art can readily distinguish the FBP1 and ßTrcp2 gene products that are useful for the presently claimed methods from those that are not and can identify many of the species of FBP1 and ßTrcp2 gene products that the claim methods encompass. Since the law does not require disclosure of a test with every species encompassed by a claim even in an unpredictable art, the specification provided an adequate description of the genus of FBP1 and ßTrcp2 gene products useful for the claimed methods. *In re Angstadt*, 537 F.2d 498, 502-503, 190 U.S.P.Q. 214, 216 (CCPA 1971).

Applicants respectfully submit that the requirement of written description is met and respectfully request that the rejection of claims 7, 13-14, 16, and 29-36 under 35 U.S.C. 112, first paragraph, be withdrawn.

B. Rejection for Lack of Enablement Should Be Withdrawn

Claims 7, 13-14, 16, and 29-36 have been rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner alleges that the specification does not reasonably provide enablement for a method of using all FBP1 and βTrcp2 proteins encompassed by the claims. In particular, the Examiner alleges that neither the specification nor the state of the art at the time the application was filed provided the necessary guidance for altering the amino acid sequences of FBP1 and βTrcp2 with an expectation of obtaining a polypeptide having the activity of FBP1 and βTrcp2 that is specified in the claims. Applicants respectfully submit that, for the reasons discussed below and according to the applicable case law, the instant specification fully enable one of skill in the art to make and use all FBP1 and βTrcp2 proteins corresponding to the scope of the presently pending claims.

The test for enablement is whether one reasonably skilled in the art could make or use the invention, without undue experimentation, from the disclosure in the patent specification coupled with information known in the art at the time the patent application was filed. *U.S. v. Telectronics Inc.*, 857 F.2d 778, 8 USPQ2d 1217 (Fed. Cir. 1988). Further, one skilled in the

art is presumed to use the information available to him in attempting to make or use the claimed invention. *See Northern Telecom, Inc. v. Datapoint Corp.*, 908 F.2d 931, 941 (Fed. Cir. 1990) ("A decision on the issue of enablement requires determination of whether a person skilled in the pertinent art, using the knowledge available to such a person and the disclosure in the patent document, could make and use the invention without undue experimentation.").

Applicants submit that the instant specification coupled with the information which was readily available to the skilled artisan at the time the instant application was filed provides considerable direction and guidance on how to make and use the claimed invention. As discussed above, claims 7 and 14 have been amended to recite, in part, methods for screening compounds using F-box Protein 1 ("FBP1") having an amino acid sequence of SEQ ID NO:2 or wherein said FBP1 is encoded by a nucleic acid molecule that hybridizes under moderately stringent conditions to the complement of a nucleic acid sequence of SEQ ID NO:1. New claim 37 and its dependent claims, claims 38-42; and claim 44 and its dependent claims, claims 44-48 have been added to recite, in part, methods for screening compounds using F-box protein ("FBP1") having an amino acid encoded by the FBP1 gene sequences which comprise nucleic acid molecules containing the DNA sequences of SEQ ID NO:1 and nucleic acid molecules that can hybridize to the DNA sequence of FBP1 under highly stringent conditions. Claim 7 has been amended to recite that the FBP1 and ßTrcp2 comprise at least one biological activity of endogenous FBP1 and ßTrcp2, respectively, and claim 14 has been amended to recite FBP1 and ßTrcp2 which are capable of promoting the degradation of IκBα. The screening method must be comprised of functionally active FBP1, βTrcp2, and the substrate, IκBα. Since the specification teaches the structure of FBP1 and βTrcp2 and provides assays for determining their functional activities, *i.e.*, by measuring their abilities through IκBα degradation assay, and the specification teaches one skilled in the art how to use FBP1, βTrcp2, and IκBα in accordance to with the screening methods of the instant invention to identify compounds that are useful for the treatment of proliferative and differentiative disorders without undue experimentation, the claimed invention is enabled.

Thus, Applicants submit that the specification, coupled with the state of the art as of the effective filing date of the instant application, fully enables one of skill in the art to make, use, and practice the invention as claimed without undue experimentation. Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph, be withdrawn. Similarly, new claims 37-48 satisfy the enablement requirement.

5. CLAIM REJECTIONS UNDER 35 U.S.C. § 102(b)

Claims 7, 13-14, 16, and 29-36 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Yaron et al., 1997. *EMBO J.* 16:6488-6494 ("Yaron 1997") and by Yaron et al., 1998. *Nature.* 396:590-594 ("Yaron 1998"). Applicants respectfully submit that both Yaron 1997 and Yaron 1998 fail to teach or suggest the claimed methods.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co.*, 814 F.2d 628 (Fed. Cir. 1987).

A. The Rejected Claims Are Not Anticipated by Yaron 1997

The present inventors discovered that FBP-1 and βTrcp2 are novel substrate-targeting subunits of ubiquitin ligases. In particular, FBP-1 and βTrcp2 are capable of targeting the substrate IκBα for degradation. The instant claims relate to a method for screening compounds useful for the treatment of proliferative and differentiative disorders comprising contacting a compound with a cell or a cell extract expressing both FBP-1 and βTrcp2, and the substrate, IκBα, wherein the FBP1, βTrcp2, or IκBα is recombinantly expressed; and detecting a change in FBP1 or βTrcp2 activity. Yaron 1997 does not teach or suggest that FBP1 and βTrcp2 are involved in the degradation of IκBα, thus, one skilled in the art would not know to utilize a cell or cell extract that expresses recombinant FBP1, βTrcp2 or IκBα as part of the component for an *in vitro* screening method. Yaron 1997 teaches the use of either HeLa, Jurkat, or reticulocyte cell extracts to perform *in vitro* kinase assays and *in vitro* ubiquitination assays to detect the phosphorylation, ubiquitination, and degradation of IκBα in the presence of several inhibitory peptides (*see, e.g.*, Yaron 1997 at page 6493, col. 1). HeLa cells, Jurkat cells, and reticulocytes do not naturally express a recombinant FBP-1, βTrcp2, or IκBα, and Yaron 1997 does not teach or suggest these cell lines or cell extracts produce recombinant FBP1, βTrcp2, or IκBα. Since a cell or cell extract that expresses a recombinant FBP-1, βTrcp2, or IκBα is neither expressly nor inherently described by Yaron 1997, Applicants submit that the teachings of Yaron 1997 do not anticipate amended claims 7 and 14, and the claims dependent therefrom.

Applicants respectfully request that the rejection of claims 7, 13-14, 16, and 29-36

under 35 U.S.C. § 102(b) as being anticipated by Yaron 1997, be withdrawn. Similarly, new claims 37-48 are novel over Yaron 1997 and are in condition for allowance.

B. The Rejected Claims Are Not Anticipated by Yaron 1998

Yaron 1998 fails to anticipate the instant claims because Yaron 1998 does not teach each and every element of the claims. Specifically, Yaron 1998 does not teach a method for screening compounds useful for the treatment of proliferative and differentiative disorders comprising contacting a compound with a cell or a cell extract expressing FBP-1 and βTrcp2, and the substrate, IκBα, wherein the FBP1, βTrcp2, or IκBα is recombinantly expressed; and detecting a change in FBP1 or βTrcp2 activity. In particular, Yaron 1998 does not teach or suggest a cell or cell extract wherein the FBP1, βTrcp2, or IκBα is recombinantly expressed, as required by the claims. Yaron 1998 teaches the use of HeLa cell extracts or Jurkat cells to perform assays that detect the ubiquitination and degradation of IκBα (*see, e.g.*, Yaron 1998 at page 594, col. 1; Figure 5, page 396, col. 1). HeLa cells and Jurkat cells do not naturally express recombinant FBP-1, βTrcp2, or IκBα and Yaron 1998 does not teach or suggest those cell lines or cell extracts express recombinant FBP1, βTrcp2, or IκBα. Since a cell or cell extract that recombinantly expresses FBP-1, βTrcp2, or IκBα is neither expressly nor inherently described by Yaron 1998, Applicants submit that the teachings of Yaron 1998 do not anticipate amended claims 7 and 14, and the claims dependent therefrom. Applicants respectfully request that the rejection of claims 7, 13-14, 16, and 29-36 under 35 U.S.C. § 102(b) as being anticipated by Yaron 1998, be withdrawn. Similarly, new claims 37-48 are novel over Yaron 1998 and are in condition for allowance.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the formal objections have been obviated and rejections to the pending claims should be withdrawn. No new matter has been added by these amendments. Applicants respectfully submit that all claims are now in condition for allowance. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted,

Date: October 24, 2007

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